PPTA
Plasma Protein Therapeutics Association

May 24, 2004
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Dockets Management Branch, HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

VIA E-Mail & USPS

SUBJECT: Draft Guidance, "ICH E2E: Pharmacovigilance Planning (PvP) Draft Version 4.1 dated on 11th November 2003"
Docket No. 2004D-0117

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) is pleased to provide these comments on the Food and Drug Administration's (FDA's) Draft Guidance entitled, "ICH E2E: Pharmacovigilance Planning (PvP) Draft Version 4.1 dated on 11th November 2003." [hereinafter "Draft Guidance"]. PPTA is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analog therapies. Our members provide 60 percent of the world's needs for Source Plasma and protein therapies. These include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat a complex of diseases in persons with immune deficiencies, therapies for individuals who have alpha-1 anti-trypsin deficiency which typically manifests as adult onset emphysema and substantially limits life expectancy, and albumin which is used in emergency room settings to treat individuals with shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of these medically needed life-sustaining therapies.

We also note that the Draft Guidance Document issued on May 5, 2004: Docket No. 2004D-189, "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment" contains greater detail as to policies specific to the U.S. FDA. While we have reviewed that particular Guidance document, we will reserve our opportunity to comment and mention it only to the extent that it informed our commentary on the ICH Draft Guidance.

PPTA appreciates the difficult task confronting the ICH and, overall, finds the Draft Guidance a well-written and well-organized document. The majority of our comments focus on a perceived lack of clarity or possible misunderstandings that the document, as written, could generate. Certain other areas for comment, such as the lack of definitive decision protocols, are also commented on, though we expect some clarification to take place as we review the 2004D-189 Draft Guidance mentioned above, noting as well that

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the ICH efforts are meant to "encourage harmonization and consistency." (Sec. 1.2, Background) The major areas for comment in the ICH document, however, are: 1) definitional issues; 2) privacy laws; 3) issues relating to the expected resource outlay for costly studies; 4) issues relating to current reporting mechanisms; and 5) potential tort liability. These five areas intersect in certain spots, and it could be that a resolution of a particular issue could resolve others; conversely, care must be taken to ensure that a change in one section does not confuse another.

1. Definitional Issues

PPTA expects that some of the definitional issues can be resolved by drawing attention to certain modules within the Common Technical Document (CTD). For example, Section 2 (Pharmacovigilance Specification) instructs the reader to cross-reference Sections 2.5.5, 2.5.6, and 2.7.4 when organizing content for the Specification: identified risks, potential for important unidentified risks, potentially at-risk populations, and situations not adequately studied. While Module 5 of the CTD, containing some definitional guidance, words used in the Draft Guidance like "special," "important," "serious," and so on, are used without definition or comparison. This is also assuming that the term "adverse event" is used consistently through the ICH modules.

Illustrative is CTD Section 2.7.4.1.3, wherein the word "special" is used in terms of a study population and characteristics such as hospitalization and impaired renal function are used to describe a "special" instance. Within the Draft Guidance, however, the word "special" should at least cross reference a section in the CTD or other related document. The best approach would be to define modifiers such as "special" or "important" in the Draft Guidance.

Section 3 (Pharmacovigilance Plan) contains the word "important" as an operative descriptive term for "potential risks," begging the question of defining important and non-important risks. The Sections of the CTD alluded to above do not provide adequate elucidation of the "important" domain and should also be defined. "Routine" pharmacovigilance is also nebulous, especially when it comes into comparison with the heightened pharmacovigilance triggered by a "special" characteristic or "important" adverse event.

2. Patient privacy

PPTA notes that the Draft Guidance states that "[t]he highest possible standards of professional conduct and confidentiality should always be maintained and any relevant national legislation on data protection followed." (p. 6) In the recent FDA "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment," it is stated that "The Privacy Rule [45 CFR §§160, 164(a), 164(e)] specifically permits covered entities to report adverse events and other information related to the quality, effectiveness, and safety of FDA-regulated products both to manufacturers and directly to FDA. . . ." (fn. 3).

PPTA also is of the understanding that a drug sponsor is not a "covered entity" within the meaning of the Privacy Rule.

However, PPTA would ask that the study designs presented in the Draft Guidance be reviewed to ensure congruence with laws respecting data confidentiality and patient information. In the United States, state law plays an active part in protecting patient information as well as federal law. While the Privacy Rule gives no private right of action (45 CFR §160.522) and pre-empts conflicting state law, it allows the Secretary of Health and Human Services to review and make exceptions for areas of state law that "is necessary" (45 CFR §160.203(a)(1)) or when a state law "relates to the privacy of individually identifiable health information and is more stringent than [federal statute or regulation.]" (45 CFR §160.203(b)(2)) PPTA is concerned that the Draft Guidance's enthusiasm for methods of "data mining" and endorsement of "intensified" reporting, registries, and active surveillance, while well-meaning, could lead to civil liability for a study sponsor in either the form of state enforcement action or private lawsuits.

Indeed, even should the study sponsor prevail in such an action, the cost of defending the study through prolonged discovery or trial could very well act as a deterrent for performing "data mining" or similar study. The costs of the litigation itself could be crippling. PPTA urges the review of the suggested methods of surveillance and issuance of a companion document to aid a study sponsor in determining rights and duties under differing patient privacy regimes. We would also ask that greater emphasis be placed on adherence to privacy regulations within the Draft Guidance itself, as it is not in a particularly prominent position in the narrative. We suggest that FDA add a cautionary note to the Draft Guidance warning the reader that state laws may be more stringent than federal, and that study designs should be reviewed within state and local requirements as well as federal.

As a case in point, the California state government recently passed a statute amending its state privacy regulations, "impact[ing] the ability of pharmacies, pharmacy benefit managers, and pharmaceutical manufacturers to distribute informational mailings to consumers." (See *The Continuing Evolution of Patient Privacy: California Legislation Impacts Drug Marketing*, by David J. Bloch and Daniel A. Cody, FDLI Update, May/June 2004.) The California Act applies to pharmaceutical marketing and is intended to work in concert with HIPAA; currently, its impact is unknown. The salient point, however, is that the Privacy Rule and HIPAA do not represent the entire universe of patient privacy. PPTA is concerned that the Draft Guidance ignores this and would ask that this area of the Draft Guidance be improved.

3. Resource outlay

PPTA notes that the suggested study designs in the Draft Guidance appendix move from the simplest reporting requirement to complex longitudinal studies. While the statistical power of the hypotheses that can be generated from the more multifaceted

studies is undisputed, the costs of these exercises can skyrocket with every layer of complexity added.

The current FDA adverse event reporting system captures many problematic areas and safety signals that occur once a therapy is approved and distributed; it could also be noted that many drug sponsors over-report safety signals in the interest of patient safety. It then begs the question of whether a complicated longitudinal study, as clearly preferred in the Draft Guidance, would truly capture a significantly larger number of safety signals that are related to therapeutic use.

As mentioned above, the statistical power of such a study cannot be denied. However, given the definitional issues listed above, it would be clearly preferable to have a clearer decision protocol on the institution of a pharamacoepidemiology study. The Draft Guidance generally observes that such a study should be commensurate with many factors, including the type of therapy, the intended population, special considerations, and so forth, but the decisional matrix envisioned seems to lean toward a case-by-case approach that does not lend itself to a uniform or harmonized method.

PPTA certainly appreciates the flexibility present in the current document. However, we believe that this flexibility can lead to problems between competing entities and would appear to lack a cohesive theme upon which reliance can be placed.

4. Current reporting mechanisms

We note that patient safety and adverse event reporting has been studied thoroughly and recently by the U.S. Institute of Medicine in *Patient Safety: Achieving a New Standard of Care* (National Academies Press, 2004). That publication provides an interesting case study:

> If an individual suffered a serious adverse drug event (ADE) in a New York hospital, the clinician would first file a report internally for review by the designated hospital representative. A second report would be filed with the New York State Department of Health through NYPORTS. Another third report could be voluntarily submitted to the [FDA], either through the FDA MedWatch reporting system or through private-sector organizations such as the United States Pharmacopia (USP), to inform the FDA of potential serious problems with the drug. Adding further to the burden of disparate and multiple methods for representing an ADE are the voluntary reporting requirements of the hospitals' accrediting organization, the Joint Commission for Accreditation of Healthcare Organizations (JCAHO), whose proposed taxonomy provides yet another dataset for classifying and reporting such events. Already this example involves

four different reports with varying data elements for the same ADE. (pp. 280-281)

The IOM Report also notes that FDA itself uses two different sets of terminology for clinical trials and post-marketing surveillance and allows other organizations to report events using still different terminology. "Thus, for the FDA alone, the data related to one particular ADE is represented by three different data sources." (p. 281) All of these terminological differences require cross-referencing and mapping. When compounded with the definitional problems in the international domain and the ones specifically mentioned above in the Draft Guidance, the problem grows in geometric proportions.

The IOM proposal is "the development of a common reporting format of domain areas, data elements, and terminologies that would serve as a common language for reporting, research, and analysis on patient safety." (pp. 281-282) While PPTA has not studied the ramifications of that proposal in detail, we would like to note that the Draft Guidance does little to alleviate the problems described by IOM. The CTD is in itself a lengthy and complex work and again should be cross referenced in the guidance.

PPTA also notes that the new FDA Draft Guidance, "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment," the AERS and VAERS system, along with voluntary reporting, are emphasized as methods for which a case series of safety signals should be developed. Neither the ICH Draft Guidance nor the FDA Draft Guidance addresses the difficulties experienced by clinicians and sponsors described in the IOM report. PPTA would ask that the IOM concerns be addressed through an Agency-industry partnership that allows more streamlined reporting systems, before the decisional review process becomes entrenched toward institution of complicated longitudinal studies that may actually complicate, rather than solve, adverse event report ascertainment.

5. Liability

PPTA is uncomfortable with the notion that seems to be present in the Draft Guidance, that both the Agency and a drug sponsor would knowingly place into the marketplace a therapy that has unidentified but somehow "important" risks. PPTA wonders how an "unidentified" risk can still be identified as "important." Making an allowance for unquantified, unqualified, and unverified risk is understandable, but the phraseology present in the Draft Guidance seems to operate in a vacuum ambivalent to a world in which lawsuits are commonplace.

PPTA member companies, like many in the biological therapeutic and chemical entity pharmaceutical industries, perform cutting-edge research and take great pains to ensure the robustness of clinical trials, along with high levels of safety and efficacy of the final product. Asking that a company create a document that "is a summary of the identified risks of a drug, *the potential for important unidentified risks*, the populations

potentially at risk and *situations that have not been adequately studied*" (Part 2, Pharmacovigilance Specification, emphases added) may be construed in such a way as to be asking that same company to make an unwarranted admission that can raise a direct inference of negligence. This same admission would be contained in a document readily available in discovery, by subpoena, deposition, or request for documents.

In the unlikely event of an adverse reaction, the argument could *always* be made that the reaction was the result of inadequate study. The Draft Guidance seems to give governmental imprimatur and endorsement of a finding of negligence on the part of a drug sponsor. PPTA would ask that these requirements be re-worked so as to not conclude negligence on the part of a therapy's sponsor before a product has yet to be marketed.

6. Summary

PPTA appreciates the opportunity to comment on the Draft Guidance. We have voiced concerns of varying levels with regard to some of the provisions within the Draft Guidance, including associated costs, patient privacy, definitional issues, difficulties in the current reporting regime, and liability. We would be willing to engage in further discussion should the Agency have questions or concerns. We support the effort toward international harmonization and look forward to working with other interested parties toward that goal.

Respectfully submitted,

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